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Correlation vitamin D deficiency with obesity and impaired glucose metabolism in women with polycystic ovary syndrome

Korelasi defisiensi vitamin D dengan obesitas dan gangguan metabolisme glukosa pada wanita dengan polikistik ovarium sindrom

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Abstract

Vitamin D deficiency is a worldwide problem, particularly in Indonesia. Obesity and impaired glucose metabolism have an impact on vitamin D status in women with polycystic ovarium syndrome and are still controversial. This study aimed to examine vitamin D levels and the correlation between obesity and impaired glucose metabolism in PCOS patients. This research employed analytical observational techniques with a case-control approach with 40 women diagnosed with Rotterdam Criteria PCOS in Mother and Child Hospital Kasih Ibu Tegal during September-October 2023. This study used the Chemiluminescent Mikropartikel Immunoassay (CMIA) method to measure vitamin D levels in the laboratory. The statistical test utilized were Shapiro-Wilk, Paired T-Test and Mann Whitney and Chi Square. Results: There was no significant difference in the serum 25(OH)D levels between women with PCOS and controls (p>0,05; p=0,745). The group of patients with an obese waist circumference was 9.75 times more likely to develop PCOS than the group with a normal waist circumference (OR = 9,75; 95% CI = 1,16-82,11; p = 0,013). In conclusion, there was no substantial variation in vitamin D levels between PCOS and non-PCOS patients. Vitamin D deficiency correlates with obesity but does not correlate with impaired glucose metabolism.

Keywords: Vitamin D, impaired glucose metabolism, polycystic ovary syndrome, obesity

Abstrak

Vitamin D defisiensi adalah masalah diseluruh dunia termasuk di Indonesia. Obesitas dan gangguan metabolisme glukosa berdampak pada status kadar vitamin D pada wanita dengan polikistik ovarium sindrom namun masih kontroversial. Penelitian ini bertujuan untuk menginvestigasi status vitamin D dan menganalisa korelasi obesitas dan gangguan metabolisme glukosa terhadap wanita dengan PCOS. Metodologi: Penelitian ini adalah penelitian *observasional analitik* dengan pendekatan kasus kontrol. Desain studi kasus kontrol dengan 40 wanita yang didiagnosa PCOS dilakukan RSIA Kasih Ibu Tegal pada September-Oktober 2023.Pada Penelitian ini dilakukan pemeriksaan laboratorium kadar vitamin D dengan metode Chemiluminescent Mikropartikel Immunoassay (CMIA). Analisis statistik mengunakan Shapiro -Wilk, Paired T- Test, Mann Whitney dan Chi Square. Hasil kadar serum 25 (OH) D tidak signifikan lebih rendah pada wanita dengan PCOS dibanding kontrol *(p>0.05; p=0,745)*. Kelompok subyek dengan lingkar pinggang obesitas memiliki resiko untuk mengalami PCOS 9,75 kali lebih besar dibandingkan dengan subyek dengan lingkar pinggang normal (OR = 9,75; CI 95% = 1,16-82,11; *p*= 0,013). Kesimpulan: Data penelitian ini menunjukan belum memberikan perbedaan yang bermakna terhadap kadar vitamin D pada pasien PCOS dan Non

PCOS. Vitamin D defisiensi berkorelasi dengan obesitas namun tidak berkorelasi dengan gangguan metabolisme glukosa.

Kata Kunci: Vitamin D, gangguan metabolisme glukosa, polikistik ovarium sindrom, obesitas,

Introduction

The main cause of infertility in women of reproductive age is polycystic ovary syndrome (PCOS). The frequency of women with polycystic ovarian syndrome is 52% in Southeast Asia (Holick, 2017). Polycystic ovaries have been diagnosed using two of the three Rotterdam criteria since 2003: oligo-anovulation or chronic anovulation; clinical and/or biochemical manifestation of hyperandrogenemia; and the appearance of polycystic ovaries, specifically polycystic eggs such as cart wheels, on transvaginal ultrasound (Wang et al., 2020). Obesity, hyperandrogenism, and insulin resistance are the characteristics of polycystic ovary syndrome. An increased risk of developing type 2 diabetes mellitus, metabolic disorders, and cardiovascular diseases is linked to polycystic ovary syndrome study.

Vitamin D, a nutrient included in the steroid hormone, is crucial for reproductive function, as it affects ovarian follicle development, luteinization, and the ability of granulosa cells to produce progesterone (Berry et al., 2022). Vitamin D insufficiency is a widespread issue affecting people worldwide, including Indonesia. Women with polycystic ovarian syndrome frequently have vitamin D insufficiency. Individuals diagnosed with polycystic ovarian syndrome who are obese exhibit 70–80% insulin resistance, but those diagnosed with the illness who are thin exhibit only 20–25% insulin resistance (Joham et al., 2016).

Hyperandrogenism and insulin resistance play major roles in the pathophysiology of ovulation abnormalities in obese patients (Lips et al., 2019). Obesity is a major health risk factor that adds a socioeconomic burden to the global public health system (Hadi et al., 2020). Obesity is a chronic low-grade inflammation that secretes inflammatory markers, such as TNFα, leptin, IL-6, and adiponectin. Intestinal microbial flora are metabolic organs involved in obesity and metabolic disorders through various signaling pathways (Asgharian et al., 2017). Vitamin D may influence the gut microbiota by improving gut barrier function and suppressing inflammation and epithelial cell apoptosis (Magne et al., 2020).

Vitamin D receptors are expressed in 2776 genomic positions and modulate the expression of 229 genes in more than 30 different tissues, such as the skeletal, brain, pancreas, immune cells, and ovary. Vitamin D may play a role in glucose metabolism by enhancing insulin synthesis and release, increasing insulin receptor expression, or suppressing proinflammatory cytokines that may contribute to impaired glucose metabolism, such as hyperinsulinemia (Shang & Sun, 2017).

This study was conducted in Tegal City for the first time. To date, there have been no studies on vitamin D deficiency in women with PCOS. Vitamin D deficiency is common in woman with or without PCOS(Joham et al., 2016). The relationship between vitamin D, PCOS, and metabolic conditions such as obesity and impaired glucose metabolism is still under debate (Ng et al., 2017). In Indonesia, little information is available on the vitamin D status of women with polycystic ovarian syndrome. This study aimed to measure vitamin D levels and determine the correlation between vitamin D deficiency, obesity, and impaired glucose metabolism in women with PCOS.

Methods

Study Desain and Participant

This study used a case-control methodology. A simple random sample was used as the control, whereas fixed disease sampling was used for the case participants. Forty women were diagnosed with Rotterdam. Among these requirements is the polycystic ovary syndrome (PCOS). Participants were chosen between September and October 2023 from the Mother and Child Hospital Kasih Ibu Tegal. Forty women without PCOS were included as controls. We employed the modified Rotterdam criteria as diagnostic criteria for PCOS (Singh et al., 2017). Women who used oral contraceptives for three months and had congenital adrenal hyperplasia, autoimmune diseases, thyroid diseases, or parathyroid diseases were excluded. Based on ethical clearance, No. No. 418/EC/KEPK/FKUNDIP/VIII/2023 and in cooperation with the Paramitha Laboratory, the procedure was approved by the Ethics Commission of the Faculty of Medicine, Diponegoro University.

Outcome Measures

In-person interviews were conducted with each participant, who received a questionnaire. Data on many characteristics including blood pressure, waist circumference (WC), body mass index (BMI), and age. Basic data, such as anthropometric assessments, were collected by skilled interviewers following a defined process. Waist circumference was measured by standing halfway between the iliac crest and lower costal border. Body mass index (BMI) for the Asian population was calculated using the following WHO criteria: healthy weight (18,5 <23 kg/m2), overweight (23,0 <25 kg/m2), and obese (>25 kg/m2) (WHO, 2004). Body mass index (BMI) was calculated as the weight (kg)/height squared (m^2).

Venous blood was drawn for a variety of tests, such as the measurement of serum 25-hydroxyvitamin D (25(OH)D). According to the Institute of Medicine, women with a concentration of 20–30 ng/mL were considered to have vitamin D insufficiency, whereas serum 25(OH)D levels below 20 ng/mL were considered to indicate vitamin D deficiency. Serum 25(OH)D levels of 30–50 ng/mL were considered normal (Yun et al., 2017).

Both fasting blood glucose and oral glucose tolerance tests were used to identify blood glucose indicators. According to the American Diabetic Association (ADA, 2018), a normal oral glucose tolerance test (OGTT) is defined as less than 140 mg/dl, and a normal fasting blood glucose level is defined as less than 100 mg/dl. The first result was the variation in vitamin D levels between the PCOS and control groups. The correlations between obesity and poor glucose metabolism in women, as well as serum 25(OH)D levels, were secondary results.

Statistical Analysis

The data were analyzed using SPSS 24.0. Continuous variables are expressed as the mean ± SD. Numbers (%) were used to represent categorical parameters, and distribution data were examined using the Shapiro-Wilk test. The Mann-Whitney non-parametric test was used to examine the variation in 25(OH)D concentration between PCOS-affected women and controls. Chi-square test was used to examine the relationship between vitamin D insufficiency, obesity, and decreased glucose tolerance. Statistical significance was set at p-value < 0,05.

Result and Discussion

Overall, 80 participants were included in the study (Table 1).

Table 1. Characteristics subject (n= 80)

Characteristics Subject	n (%)
Subject	
PCOS	40 (50,0)
Control	40 (50,0)
Age (year)	29,22 ± 4,27
Menstrual History	
Non Regular	36(45,0)
Regular	44(55,0)
Physical Activity	
Non Sedentary	42(52,5)
Sedentary	38(47,5)
Height (cm)	156,00 ± 4,00
Weight Badan (kg)	58,50 ± 16,75
BMI (kg/m²)	24,40 ± 6,47
<18,5 (Less)	6(7,5)
18,5 – 22,9 (Normal)	25(31,3)
23 – 34,9 (Over)	10(12,5)
>25 (Obesity)	39(48,8)
Viceral Fat	8,50;7,25
Total Fat	32,07 ± 4,43
Muscle Mass	27,54 ± 2,75
Body Age	37,74 ± 9,48
Waist Circumference	93,15 ± 11,71
Obesity	71(88,8)
Normal	9(11,3)
Fasting Blood Glucose	83,17 ± 11,43
TTGO	126,16 ± 19,72
Impaired Glucose Metabolisme	
Yes	5(6,3)
Normal	75(93,8)
Vitamin D	13,97 ± 5,72
<20	69(85,2)
20 - 30	12(14,8)

BMI=body mass index, kg=kilogram, cm=centimeter, m=meters, %= persentage.

This table demonstrates the baseline features of the women in the two categories. Total fat, age, body age, waist circumference, fasting blood glucose, oral glucose tolerance test, and vitamin D levels were normally distributed, and the data are presented as mean± SD. Meanwhile, height, weight, BMI, and visceral fat did not have normally distributed data; therefore, we used the median. Menstrual cycle, physical activity, BMI, waist circumference, impaired glucose metabolism, and vitamin D levels were presented as n (%).

Table 2. The difference characteristic subject PCOS (n= 40) and controls (n= 40)

Characteristics Subject	PCOS n (%)	Control n (%)	p-value	OR(95%CI)
Menstrual History [c]				
Non Regular	27(67,5)	9(22,5)	0,000**	7,15(2,65 – 19,34)
Regular	13(32,5)	31(77,7)		
Physical Activity [c]				
Non Sedentary	13(32,5)	29(72,5)	0,000**	0,18(0,07 – 0,48)
Sedentary	27(67,5)	12(27,5)		
Body Mass Index [c]				
<18,5 (Less)	1(2,5)	5(12,5)	0,000**	Ref,
18,5 – 22,9 (Normal)	8(20,0)	17(42,5)		0,42(0,04-4,26)
23 – 34,9 (Over)	1(2,5)	9(22,5)		1,80(0,09-35,42)
>25 (Obesity)	30(75,0)	9(22,5)		0,06(0,01-0,58)
Waist Circumference [b,c]				
Obesity	39(97,5)	32(80,0)	0,013*	9,75(1,16 – 82,11)
Normal	1(2,5)	8(20,0)		
Impaired Glucose Metabolism [c]				
Yes	4(10,0)	1(2,5)	0,166	4,33(0,46 – 40,61)
No (Normal)	36(90,0)	39(97,5)		
Vitamin D [b,c]				
<20	34(85,0)	35(87,5)	0,745	0,97(0,28 – 3,31)
20 - 30	6(15,0)	5(12,5)		

**p<0,05, *p,0,01* [b]*Independent t-test,* [c] *Chi Square*

Basic Characteristic of the Studied Group

The differences between the characteristics of the PCOS and Control groups were determined by comparing their respective characteristics (Table 2) and displaying the features that differed between the PCOS and Control groups. Since all data in the PCOS and Control groups were less than 50, a data normality test using the Shapiro–Wilk test was performed prior to the difference test.

The Mann-Whitney U test was used to test non-parametric data because the following variables had non-normal distributions: age, height, weight, visceral fat, muscle mass, body age, waist circumference, fasting blood sugar,oral glucose tolerance test, and vitamin D. Parametric tests, specifically the independent t-test, were used to assess BMI and total fat data. P values < 0.05 in the difference test indicate a significant difference. The non-PCOS control and PCOS groups did not differ significantly in terms of age, height, impaired glucose metabolism, or vitamin D concentration (p >0,05).

Correlation of Vitamin D With Metabolic Risk Factor (Obesity and Impaired Glucose Metabolism)

If the p-value was < 0,05, there was a significant difference between the PCOS and Control groups; however, if the p-value was > 0,05, there was no significant difference. Chi-square test, a test used to determine the association between two variables using categorical and categorical data types; if the p-value is less than 0,05, it can be determined that there is a significant link; if the p-value is greater than 0,05, there is no significant relationship.

Table 2 indicates that the body weight of the PCOS group was notably greater than that of the control group (66,65; 19,40 vs. 54,14 ± 8,38, p <0,05). The BMI of the PCOS group was notably greater than that of the control group (27,37 ± 5,34 vs, 22,48 ± 3,33, p value <0,05), The amount of visceral Fat in the PCOS group was considerably higher than that in the control group (10,15, 7,88, 5,50, and 5,38, respectively; p <0,05). The PCOS Group had significantly higher levels of total fat, muscle mass, body age, waist circumference, fasting blood sugar, and OGTT results than the control group. There was a significant relationship between Menstrual History, BMI, and Waist Circumference with PCOS, according to the odds ratio (OR) value.

The data in Table 2 show that respondents with irregular menstruation are 7,15 times more likely to have PCOS than those with normal menstruation. Respondents with Obese Waist Circumference were 9,75 times more likely to have PCOS than those with Normal Waist Circumference. Impaired glucose metabolism and PCOS were not significantly correlated with one another. Neither the association between Vitamin D and PCOS nor the difference in Vitamin D levels between the PCOS and Control groups were statistically significant.

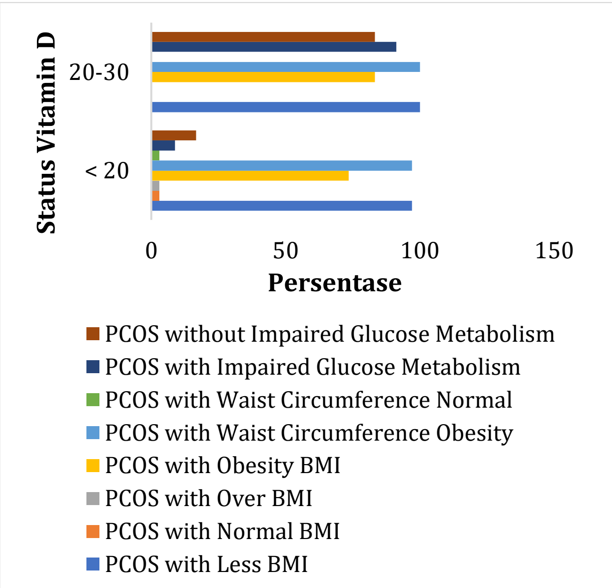

Figure 1. Vitamin D status in PCOS without impaired glucose metabolism and with impaired glucose metabolism

Table 3 shows that vitamin D concentration was highest in BMI with over category and vitamin D concentration lowest in BMI with less category. There was no difference in vitamin D concentration based on Body Mass Index in PCOS group (p>0,05).

Table 3. The difference concentration vitamin D with metabolic risk factor in PCOS

Variable	Vitamin D	p
BMI[d]		
<18,5 (Less)	9,00 ;	
18,5 – 22,9 (Normal)	14,22 ± 7,15	0,797
23 – 34,9 (Over)	16,40; ,	
>25 (Obesitas)	14,51 ± 5,36	
Waist Circumference[b]		
Obesitas	14,58 ± 5,50	0,128
Normal	5,90;	
Impaired Glucose Metabolism[b]		
Yes	16,30 ± 3,79	0,473
No (Normal)	14,14 ± 5,77	

[b]Mann-whitney, [d]Analysis of Variance

Vitamin D Status With Metabolic Risk Factor (Obesity and Impaired Glucose Metabolism)

Table 3 shows that the majority of respondents with Vitamin D levels < 20 or 20 – 30 were in the PCOS group with a low BMI. The PCOS group without impaired glucose metabolism included the majority of respondents with a vitamin D status of <20, whereas the PCOS group with impaired glucose metabolism included individuals with a vitamin D status between 20 and 30. In Figure 1, a p value > 0.05 indicates that there is no significant correlation between the respondents with impaired glucose metabolism and their vitamin D levels.

As shown in Figure 1, there was no significant relationship between Vitamin D status and BMI in PCOS respondents, as seen from the p-value > 0.05. Most respondents with a Vitamin D status < 20 or 20 – 30 were in the PCOS group with Waist Circumference Obesity. (Figure 1) There was no significant relationship between Vitamin D status and BMI in the PCOS group (p > 0.05).

In this study, the sample's age was distributed in the adult category, with age intervals indicating that the majority of the research subjects in the control and case groups were aged between 25 and 33 years. This age range is suitable for reproductive-aged women who menstruate. Women in this age range experience folikulogenesis. Woman in 25-33th should have regular menstruation and folikulogenesis; however, women with infertility and PCOS usually have irregular menstruation. Vitamin D has been shown to affect reproductive tissues in animal experiments. The hypothalamic-pituitary-ovarian axis function alters vitamin D deficiency, showing oestrous cycle irregularities and resulting in arrested follicle development (Schröder-Heurich et al., 2020), and the menstrual cycle is a factor considered in the diagnosis of polycystic ovarian syndrome. Approximately 55% of the research sample comprising the study's individuals had irregular menstruation problems. Fifty-two percent of those who participated in the study and the control group either did not exercise or were sedentary. (Nasri et al., 2018)Co-supplementation strategies involving vitamin D and evening primrose oil (EPO) decreased MDA concentration, and increased glutathione (GSH) had a favorable effect on oxidative stress in PCOS. Similarly, vitamin D plus probiotics decreased hs-CRP and MDA levels, and increased TAC and GSH levels (Ostadmohammadi et al. 2019).

Table 2 shows the distribution of research participants with poor nutritional status, defined as having a Body Mass Index (BMI) value of less than 18,5 kg/m^2, as 6 people (7,5%), a group with a normal BMI value of 18, 5 kg/m^2 - 23 kg/m^2, or 25 people (31,3%), and a group with an obesity BMI value of > 25 kg/m^2 or obesity, comprising 39 people with the highest value of 48,8%. The average waist circumference of the participants ranged from 82 cm to 104 cm, On average, 88% of the research participants were obese and 93,8% did not have problems with glucose metabolism. Characteristics of research participants: Vitamin D insufficiency, defined as < 20 ng/mL, was present in 85,2% of the cases.

The majority of research participants in this study were vitamin D-deficient, a minor percentage were insufficient, and there were no participants in the normal group. In Tegal, Indonesia, there is a noteworthy incidence of vitamin D insufficiency in women with PCOS. Nonetheless, there has not been much difference in vitamin D levels between people with and without PCOS. PCOS (Mogili et al., 2018). A significant prospective observational study found a possible correlation between anovulatory infertility, vitamin D deficiency, and PCOS symptoms. Specifically, 70,03% of infertile women with PCOS had vitamin D levels < 20ng/mL. Numerous studies have into PCOS the vitamin D levels in women with PCOS. (Fang et al. 2017). Our study findings demonstrated that women with PCOS did not exhibit a statistically lower serum 25(OH)D concentration than those without the condition. Contrary to what our data indicates, several observational studies have linked low vitamin D content to higher BMI and insulin resistance in PCOS-affected women.(Muscogiuri et al., 2012). This was in conflict with our research, which demonstrated that women with PCOS who were obese or insulin-resistant had lower serum 25 (OH)D concentrations than those without these conditions (Wang et al., 2020). Studies have found that vitamin D regulates extracellular calcium, which may have an indirect effect on insulin activity (Pittas et al., 2007).

There was a substantial difference in the waist circumference between the PCOS group and the control group, as evidenced by the fact that the median and mean values of the PCOS group were larger than those of the control group (97,00, 15,25 vs. 87,00 ± 8,22, p <0,05). There was a significant difference in the fasting blood sugar levels between the two groups, as seen by the mean and median readings (87,38 ± 11,27 vs, 78,00; 11,75, p value <0,05) for the PCOS group and higher values for the Control group.

A p value of less than 0,05 indicates a significant difference in the oral glucose tolerance test findings between the PCOS and control groups. The mean and median scores for the PCOS group were greater than those of the control group (137,00; 29,5 versus 118,70 ± 15,19, p <0,05).

The majority of respondents with a vitamin D status of less than 20 were in this category, similar to the PCOS group without glucose metabolism issues; conversely, respondents with a vitamin D status between 20 and 30 were in this group. There was no appreciable correlation between low vitamin D levels and impaired glucose metabolism in PCOS subjects, as indicated by the fact that the p-value was > 0,05.

Obesity, oxidative stress, chronic inflammation, and metabolic syndrome are among the clinical symptoms of PCOS, and are linked to vitamin D deficiency. In our study, serum 25(OH)D levels in women with PCOS were inversely correlated with BMI, WC, and fasting blood glucose levels. Regular insulin metabolism is affected by activation of inflammatory pathways. The favorable effects of vitamin D on insulin secretion modulation and proinflammatory cytokine inhibition were shown to be affected by sugar metabolism, according to published studies (Akbari et al., 2018). In women, chronic low-grade inflammation often manifests as signs of PCOS (Dumesic et al. 2015).

A suboptimal level of vitamin D disrupts the balance of reproductive hormones, causing an accumulation of proinflammatory glycation end products (AGES) and the generation of reactive oxygen species (ROS) in the ovarian tissue, leading to aberrant folliculogenesis (Dastorani et al., 2018). Women with PCOS have been shown to benefit from vitamin D's progesterone-like effect in studies examining co-supplementation with myo-inositol. According to studies that have been published before, vitamin D treatment has been shown to dramatically lower high AMH in women with PCOS (Dastorani et al., 2018) (Dastorani et al., 2018).

Enhancements to the menstrual cycle (Irani et al., 2015)(Jafari-Sfidvajani et al., 2018). In addition, the impact of anti-inflammatory supplements on oxidative stress was found to boost the effects of high-dose vitamin D supplementation in PCOS women with IR blood hs-CRP levels (Maktabi et al., 2017)(Ng et al., 2017). Consistent with our findings, vitamin D levels were not significantly correlated with BMI, WC, or metabolic parameters in women with PCOS. This discrepancy could be attributed to variations in the sample size, participant nutrition, lodging location, season, and lifestyle during the vitamin D detection period.

The present study had several limitations. First, only a few participants were included in the study. Furthermore, Tegal, Indonesia, was the study's solitary center for PCOS. Therefore, multicenter surveys with large sample sizes in various parts of Indonesia are required to substantiate the findings of this research. Second, there were additional restrictions to this research. More specifically, no data were gathered regarding the types of foods that are high in vitamin D, the types of skin tones that can change vitamin D levels, or the quantity of sun exposure that can change those levels. (van Schoor & Lips, 2017). Third, selection of female sample only infertility population. Fourth, we did not examine the HOMA-IR gold standard for insulin resistance; we used GDP and OGTT to test impaired glucose metabolism.

When treating PCOS, serum measurements of vitamin D (25 OH), BMI, WC, GDP, and OGTT should be performed. Supplementation with calcium and vitamin D has been demonstrated to reduces oxidative stress and follicular growth (Maktabi et al., 2018).

Conclusion

In conclusion, our data demonstrated no significant difference in serum 25(OH)D levels between PCOS-affected women and controls. The vitamin D concentration was higher in the PCOS group than in the control group.

Nevertheless, vitamin D deficiency is widespread among women with PCOS in Tegal City, particularly among those who are obese and have poor glucose metabolism. Larger sample sizes and multicenter randomized controlled trials are necessary to examine the metabolic effects of vitamin D treatment in women with PCOS. Screening for vitamin D deficiency can be used in pregnancy programs and in collaboration with government programs to reduce the problem of NCDs in Indonesia.

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